PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
2002.712 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/00339	14.01.2003	21.01.2002
International Patent Classification (IPC) or both national classification and IPC		
C07J51/00		
Applicant		
AKZO NOBEL N.V. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

EPO - DG 1

12. 03. 2004

3. This report contains indications relating to the following items:

(37)

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10.07.2003	30.01.2004
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/00339

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-9 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

II - Priority

The presently claimed process of claims 1-9 relates to a method for 7α-methylation of 17β-hydroxy estra-4,6-dienes (compounds of formula (I) where n=0), 17β-hydroxymethyl-estra-4,6-dienes (compounds of formula (I) where n=1) or 19-norpregn-4,6-dien-21-ol compounds (compounds of formula (I) where n=2). This process produces to the corresponding 6-saturated, 7α-methyl compounds of formula (II) (where n=0, 1 or 2 depending on the starting material). In this regard it is noted that the process disclosed in the priority document (EP02075230) only relates to the 7α-methylation of 17β-hydroxy estra-4,6-dienes (where n=0). Consequently, the subject matter of the claims 1-9 only enjoy a right to priority within the meaning of Art.8 PCT and Art.4(H) Paris Convention in so far as they relate to the process involving the production of compounds of formula (II) where "n" is not 0 (starting from compounds of formula (I) where n=0).

Furthermore, since the intermediate product of claim 10 is not mentioned anywhere in the priority document (since it is a 19-norpregnane derivative), it also has no priority right for the same reasons as given above.

V - Reasoned statement under Rule 66.2(a)(ii) PCT

The closest state of the art with regard to the presently claimed invention consists of the following documents:

D1: US-A-3 341 557
D2*: STEROIDS (1963), 1, 317-24
D3: WO 01 58919 A

* Document D2 makes reference to document D2A (see below) in respect of certain technical features of the process disclosed in D2 (see D2, page 317, last paragraph - page 318, paragraph 1; and the scheme on page 319, where D2 makes reference to the Grignard reagent used in D2A). Consequently, according to the International preliminary examination guidelines IV, 7.1, the Grignard reagent used in the process disclosed in D2A forms an integral part of the disclosure of document D2 (this is MeMgBr plus CuCl - see D2A, page 4071, column 1, last paragraph - column 2, paragraph 1).

D2A: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 81, 1959, pages 4069-4074

The following documents are of importance in assessing the inventive step of the claimed subject matter:

D4: WO 01 05806 A cited in the application
D5: WO 01 40255 A
D6: WO 00 59920 A
D7: TETRAHEDRON LETT. (1988), 29(13), 1533-6

The following document is cited here in accordance with Rule 70.10 PCT in as far as the presently claimed invention enjoys a right to priority. In as far as the presently claimed invention does not enjoy the right to a priority (see section (II) above), this document is also relevant for the assessment of the inventive step of the presently claimed invention.

D8: WO 02 10188 A 7 February 2002 (2002-02-07)

V.N - Novelty (Article 33(2) PCT)

The presently claimed process of claims 1-9 relates to a method for 7α-methylation of 17β-hydroxy estra-4,6-dienes (compounds of formula (I) where n=0), 17β-hydroxymethyl-estra-4,6-dienes (compounds of formula (I) where n=1) or 19-norpregn-4,6-dien-21-ol compounds (compounds of formula (I) where n=2). This process produces to the corresponding 6-saturated, 7α-methyl compounds of formula (II) (where n=0, 1 or 2 depending on the starting material). The process of claims 1-9 differentiates itself over that disclosed for the production of the same compounds in documents D1, D2 and D3 in that the protecting group used in the process of claims 1-9 to protect the $-(CH_2)_n-OH$ group is a trialkylsilyl group, whereas in D1-D3, this is an acetyl group (see D1, examples 27 and 28; D2, page 317, last paragraph - page 318, paragraph 1 and page 319, scheme; D3, Figs 4 and 8). Consequently the process of claims 1-9 is novel according to Article 33(2) PCT. In every other aspect the processes of D1 and D2 are the same as those of claim 1, however, the process of D3 differs more in that a different, but equivalent methylating reagent and catalyst are used.

Feature	*Claim 1*	*D1*	*D2*	*D3*
Grignard reagent	*MeMgHal*	*MeMgBr*	*MeMgBr*	*MeLi*
Catalyst	*Copper*	*CuBr*	*CuCl*	*LiBr*

Furthermore, the intermediate compound 21-hydroxy-19-norpregn-4,6-dien-3-one is not disclosed in the state of the art, in particular document D3 discloses the corresponding 21-acetate of this compound (see D3, Fig 4, compound 9). However, this compound is protected prior to the introduction of the 6(7)-double bond (see Fig 4), and so it does not exist in the unprotected form in D3 (or anywhere else). Consequently the subject matter of claim 10 is as novel according to Article 33(2) PCT.

V.IS - Inventive Step (Article 33(3) PCT)

The problem to be solved by the presently claimed subject matter is the provision of a process for the 7α-methylation of 19-nor-steroids with a group of formula $-(CH_2)_n-OH$ in position 17β (where n=0, 1 or 2) i.e. the provision of a process for the production of compounds of formula (II). The solution to this problem consists of the process specified in claims 1-9, which differs from that of the closest state of the art documents D1-D3 in that a trialkylsilyl protecting is used instead of an acetyl group (see D1, examples 27 and 28; D2, page 317, last paragraph - page 318, paragraph 1 and page 319, scheme; D3, Figs 4 and 8). In this regard it is further noted that the use of a trialkylsilyl-protecting group for the 17β-OH group in 7α-alkylation reactions on estr-4,6-dien compounds is known from the state of the art (see D4, example 1; D5, example 5; D6, examples 1,7; D7, page 1535, last paragraph and, in as far as the claims 1-9 do not enjoy any right to a priority - see section (II) above - , D8, page 8, paragraph 2). It is consequently an evident step for the person skilled in the art to transfer this teaching of D4-D8 (that a 17β-O-trialkylsilyl protecting group can be used in 7α-alkylation reactions), over to the teaching of documents D1-D3, which leads the skilled person to replace the acetyl protecting group used in D1-D3 with the silyl protecting group used which leads to the process of claim 1. Consequently, the subject matter of claim 1 represents an obvious solution to the above mentioned problem and as such lacks

inventive step according to Article 33(3) PCT. Furthermore, the subject matter of dependent claims 2-9 does not appear to contain any further subject matter which might render these claims inventive in their own right and as such the subject matter of these claims also lacks inventive step according to Article 33(3) PCT. Furthermore, the intermediate of claim 10 does not appear in the context of an overall inventive process and as such also lacks inventive step, in particular because the allegedly characterising feature of the process of claims 1-9 (the presence of the 17ß-trialkylsily protecting group) does not manifest itself in this intermediate product. Consequently, this compound of claim 10 also lacks inventive step according to Article 33(3) PCT.

VI - Certain documents cited (Rule 70.10 PCT)

Document D8 was publsihed on 07.Feb.2002 (in the priority period see section V above), would have constituted relevant state of the art for the assessment of the inventive step for that part of the claimed invention which enjoys a priority right (see sectoin (II) above), since it teaches the use of silyl-protecting groups in the 7α-methylation process, although the process disclosed in this document differs from that disclosed in the claims of the present application in that the starting amterial and product are both 11ß-methyl substituted, which those of claims 1-9 are not.

VIII - Statement according to Rule 66.2(a)(v) PCT

The term "trialkylsilyl" as appears in claim 1. The term "alkyl" which forms an integral part of the term "trialkylsilyl" is defined on page 4, lines 28-30 of the description as being a branched or unbranched C_{1-4}-alkyl group. This does not correspond to the usual meaning of the term "alkyl", which is not limited in terms of size (number of carbon atoms). Consequently, the absence of this definition form claim 1 means that there is confusion as to the meaning of this term in claim 1, which consequently lacks clarity according to Article 6 PCT (see International Preliminary Examination Guidelines III, 4.3).